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ABOUT COVER

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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

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META-ANALYSIS

Cardiac stress testing and coronary artery disease in liver transplantation candidates: Meta-analysis

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Abstract

AIM

To evaluate the diagnostic value of dobutamine stress echocardiography (DSE) and myocardial perfusion scintigraphy (MPS) in predicting coronary artery disease (CAD) in cirrhotic patients listed for liver transplantation (LT), using invasive coronary angiography (ICA) as gold-standard.

METHODS

Retrieval of studies was based on Medical Subject Headings and Health Sciences Descriptors, which were combined using Boolean operators. Searches were run on the electronic databases Scopus, Web of Science, EMBASE, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Library for Systematic Reviews and Opengray.eu. There was no language or date of publication restrictions. The reference lists of the studies retrieved were searched manually.

RESULTS

The search strategy retrieved 322 references for DSE and 90 for MPS. In the final analysis, 10 references for DSE and 10 for MPS were included. Pooled sensitivity was 28% and 61% for DSE and MPS and specificity was 82% and 74%, for diagnosis of CAD using ICA as gold-standard, respectively.

CONCLUSION

DSE and MPS do not have adequate sensitivity for determination of whether CAD is present, despite having significant specificity.

Key words: Myocardial perfusion imaging; Coronary angiography; Liver transplantation; Echocardiography; Stress

Core tip: The concept of cardiac involvement in cirrhotic patients has been changing as patients listed for liver transplantation (LT) have become older and sicker. We aimed to evaluate the diagnostic value of dobutamine stress echocardiography (DSE) and myocardial perfusion scintigraphy (MPS) in predicting coronary artery disease (CAD) in cirrhotic patients listed for LT, using invasive coronary angiography as gold-standard. A systematic review and meta-analysis was performed, including 10 references for DSE and 10 for MPS. We concluded that DSE and MPS do not have adequate sensitivity for determination of whether CAD is present, despite having significant specificity.

INTRODUCTION

When liver transplantation (LT) programs were beginning three decades ago, it was believed that the systemic vasodilation that occurs in end-stage liver disease (ESLD) might be able to protect patients from coronary artery disease (CAD)[1]. Nevertheless, studies have shown that CAD is more prevalent in cirrhotic patients than previously suspected. In a cohort with high risk for CAD, 26% of the patients had previously unknown CAD on routine invasive coronary angiography (ICA)[2].

The cardiac profile for LT candidates has been changing, because they are now older and sicker[3]. Data from the United Network for Organ Sharing (UNOS) show that the proportion of LT recipients over the age of 65 years in the United States increased from 9.6% in 2003 to 16.3% in 2013[4]. This has been a cause for major concern regarding perioperative cardiac risk. For example, a publication from 1996 predicted that around 50% of patients with significant CAD would die from cardiac complications in the perioperative period[5]. However, in a more recent study, the presence of obstructive CAD did not significantly impact post-LT survival, when modern treatment of CAD pre-LT is taken into account[6]. Furthermore, patients with ESLD have a specific type of cardiovascular sickness, currently known as cirrhotic cardiomyopathy, whose role in LT survival is yet to be established[7].

These findings suggest a real need for protocols for cardiac evaluation of patients awaiting LT - particularly for cirrhotic patients. The American Association for the Study of Liver Diseases (AASLD) published a guideline in 2005 that recommends myocardial stress testing for every patient referred for LT[8]. Nevertheless, the guideline published in 2012 by the American Heart Association (AHA) and the American College of Cardiology (ACC)[9], suggested that myocardial stress testing should be reserved for patients with three or more CAD risk factors. A score has recently been published for evaluation of perioperative cardiac risk, but it has yet to be validated further[10].

The aim of this systematic review with meta-analysis is to summarize the evidence related to the diagnostic value of two non-invasive cardiac stress testing methods: Dobutamine stress echocardiography (DSE) and myocardial perfusion scintigraphy (MPS), for the diagnosis of CAD in cirrhotic pre-LT patients, using ICA as gold-standard.

MATERIALS AND METHODS

This study was carried out in accordance with the recommendations contained in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) guidelines[11]. Our systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), maintained by York University, on 17 August 2015 and was last updated on 5 April 2018 [registration No. 10.15124/CRD42015025391 (www.crd.york.ac.uk/prospero/)].

Data sources

Studies were retrieved using Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS), which were combined with Boolean operators. Searches were run on the electronic databases Scopus, Web of Science, Embase, Medline (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Library for Systematic Reviews and Opengray. eu. There was no language or date of publication restrictions. The reference lists of the retrieved studies were submitted to manual search. The search strategies used for each test and each database are shown in Supplemental material. Databases were last searched between August and September of 2015.

Inclusion criteria and outcomes

Cohort or case-control studies were eligible for selection, hence it was analyzed the diagnostic accura-

cy of DSE and/or MPS in adult patients with cirrhosis submitted for pre-LT evaluation. The tests had to be performed as a part of cardiac evaluation before LT. Studies were excluded if they did not meet these inclusion criteria. If there was more than one study published using the same population, the most recent study was selected for the analysis. Studies published only as abstracts were included, as long as the data available made analysis possible. The outcome measured was a diagnosis of CAD using ICA as gold standard.

Study selection and data extraction

An initial screening of titles and abstracts was the first stage to select potentially relevant papers. The second step was the analysis of the full-length papers. Two independent reviewers (Jonathan Soldera, Fabio Camazzola) extracted data using a standardized data extraction form after assessing and reaching consensus on eligible studies. The same reviewers separately assessed each study and extracted data about the characteristics of the subjects, the diagnostic accuracy for DCE and MPS and the outcomes measured. A third party (Santiago Rodriguez) was responsible for divergences in data extraction, clearing them when required. Quality of evidence regarding diagnostic accuracy was evaluated according of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[12].

Statistical analysis

In anticipation of possible heterogeneity between the populations of the studies, a random-effects Der-Simonian and Laird model was used. Data regarding the tests' diagnostic accuracy was collected. The measures of diagnostic accuracy chosen were specificity, sensitivity, likelihood ratio and diagnostic odds ratio. Heterogeneity was assessed using the I^2 statistic. MetaDisc 1.4 was used for diagnostic accuracy. The small number of studies included made funnel plot analysis impossible.

RESULTS

Systematic review

The search strategy retrieved 322 references for DSE and 90 for MPS. After analyzing titles and abstracts, 111 references for DSE and 24 for MPS were excluded because they were duplicates and the full texts were retrieved for 60 references on DSE and 26 on MPS. In the final analysis, 10 references were included for DSE and 10 for MPS. Flowcharts illustrating the search strategies are shown in Supplemental Figures 1 and 2, respectively. Studies included were either a case-control study or a prospective or historical cohort study.

DSE

Data were collected after the conclusion of a systematic review of the 10 studies included in the diagnostic analysis that used ICA as the gold-standard. The data extracted are summarized in Table 1.

A minority of the patients included in these studies underwent ICA and they were generally higher risk patients with positive DSE findings or multiple risk factors. Data for risk factors specifically for the patients who underwent ICA were not available for most studies, therefore the data on risk factors described refer to the whole study population, as summarized in Supplemental Table 1.

The initial meta-analysis was performed including all studies. Global sensitivity was 28% [95% confidence interval (CI): 21.2%-35.6%] with high heterogeneity (I^2 = 69%) (Figure 1), specificity was 82.9% (95%CI: 78.5%-86.8%) with high heterogeneity (I^2 = 84.1%) (Figure 2) and the diagnostic odds ratio was 2.09 (95%CI: 0.96-4.58) with moderate heterogeneity (I^2 = 47.5%) (Supplemental Figure 3). The positive likelihood ratio was 1.7 (95%CI: 1.06-2.7) with moderate heterogeneity (I^2 = 51.4%) (Supplemental Figure 4) and the negative likelihood ratio was 0.92 (95%CI: 0.81-1.04) with little heterogeneity (I^2 = 18.8%) (Supplemental Figure 5). An asymmetrical Receiver Operating Characteristic (ROC) curve is provided in Supplemental Figure 6.

A meta-regression was performed using the subsets of patients from each of the study samples who had undergone ICA and no statistically significant association was detected between this variable and the diagnostic odds ratio (P = 0.0586).

In order to attempt to reduce heterogeneity between studies, a sub-analysis was performed of sensitivity and specificity according to the definition of a positive ICA result employed by each study. Studies that used a positive ICA defined as any number of lesions with at least one greater than 70%, had a sensitivity of 21% (95%CI: 13.4%-31.3%) with high heterogeneity (I^2 = 71%) and a specificity of 91.5% (95%CI: 86.8%-95%) with high heterogeneity (I^2 = 63.5%), while studies that defined positive ICA as any number of lesions, with at least one greater than 50%, had a sensitivity of 36.1% (95%CI: 25.1%-48.3%) with high heterogeneity (I^2 = 66.3%) and a specificity of 69.9% (95%CI: 61.4%-77.6%) with high heterogeneity (I^2 = 68%).

MPS

Data were collected after conclusion of a systematic review of the 10 studies included in the diagnostic analysis that used ICA as the gold-standard. The data extracted are summarized in Table 2.

As with DSE, a minority of the patients included in these studies underwent ICA, and they were generally

Table 1 Studies included in analysis - dobutamine stress echocardiography

Ref.	TP	FP	FN	TN	Total number of patients in the study	Proportion of patients who underwent ICA	Definition of patients included	Criteria for ICA indication	Lesion for definition of positive ICA	QUADAS-2 quality analysis criteria
Ibrahim *et al*[13]	5	8	5	22	366	10.9%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	NA	RB: P + I - R + F ? AC: P + I ? R +
Donovan *et al*[14]	3	6	1	8	190	9.5%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 50%	RB: P + I + R + F + AC: P + I + R +
Findlay *et al*[15]	1	6	0	0	117	6%	Cirrhotic patients in pre-LT evaluation	Transplanted patients	> 70%	RB: P + I + R + F + AC: P - I + R +
Harinstein *et al*[16]	2	7	14	41	105	61%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 70%	RB: P + I + R + F + AC: P + I + R +
Harinstein *et al*[16]	4	5	20	35	105	61%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 50%	RB: P + I + R + F + AC: P + I + R +
Plotkin *et al*[17]	2	0	0	19	40	52.5%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 70%	RB: P + I + R + F + AC: P + I + R +
Ramrakhiani *et al*[18]	4	10	0	0	201	7%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 70%	RB: P + I - R - F ? AC: P + I - R -
Tsutsui *et al*[19]	2	5	0	10	230	7.4%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 50%	RB: P + I + R + F + AC: P + I + R +
Umphrey *et al*[20]	0	0	0	9	157	5.7%	Cirrhotic patients in pre-LT evaluation	High risk patients	> 70%	RB: P + I + R + F + AC: P + I + R +
Snipelisky *et al*[21]	12	16	20	18	66	100%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 50%	RB: P + I + R + F + AC: P + I + R +
Patel *et al*[22]	15	10	56	124	420	48.8%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive DSE	> 70%	RB: P + I + R + F + AC: P + I + R +

TP: True positive; FP: False positive; FN: False negative; TN: True negative; ICA: Invasive coronary angiography; LT: Liver transplantation; DSE: Dobutamine stress echocardiography; NA: Not available; QUADAS-2: Quality assessment of diagnostic accuracy studies-2; RB: Risk of bias; P: Patient selection; I: Index text; R: Reference standard; F: Flow and timing; AC: Applicability concerns.

higher risk patients with a positive MPS result or multiple risk factors. As with DSE, data for risk factors specifically for the patients who underwent ICA were not available for most studies, therefore the data for risk factors described refer to the whole study population, as summarized in Supplemental Table 2.

The diagnostic data were used for meta-analysis. The initial meta-analysis was performed including all studies. Global sensitivity was 61.8% (95%CI: 50%-72.8%) with high heterogeneity (I^2 = 69.8%) (Figure 3), specificity was 74.3% (95%CI: 70.2%-78.2%) with high heterogeneity (I^2 = 77.1%) (Figure 4) and the diagnostic odds ratio was 4.74 (95%CI: 1.51-14.8) with high heterogeneity (I^2 = 61.9%) (Supplemental Figure 7). The positive likelihood ratio was 2.26 (95%CI: 1.47-3.48) with high heterogeneity (I^2 = 63.5%) (Supplemental Figure 8) and the negative likelihood ratio was 0.57 (95%CI: 0.32-1.02) with high heterogeneity (I^2 = 62.7%) (Supplemental Figure 9). An asymmetrical ROC curve is

provided in Supplemental Figure 10.

A meta-regression was performed using the sub-sets of patients from each of the study samples who had undergone ICA and no statistically significant association was detected between this variable and the diagnostic odds ratio (P = 0.4984).

In order to attempt to reduce heterogeneity between studies, a sub-analysis was performed of sensitivity and specificity according to the definition of a positive ICA result employed by each study. Studies that used a positive ICA defined as any number of lesions with at least one greater than 70% had a sensitivity of 59.4% (95%CI: 46.4%-71.5%) with high heterogeneity (I^2 = 70.5%) and specificity of 76.3% (95%CI: 71.6%-80.5%) with high heterogeneity (I^2 = 80%). In another sub-analysis, including only the four studies in which ICA was performed for all patients, sensitivity was 57.1% (95%CI: 44%-69.5%) with high heterogeneity (I^2 = 71.1%) and specificity was 75.5% (95%CI: 71.4%-79.7%) with high heterogeneity (I^2 =

Table 2 Studies included for analysis - myocardial perfusion scintigraphy

Ref.	TP	FP	FN	TN	Total number of patients in the study	Proportion of patients who underwent ICA	Definition of patients included	Criteria for ICA indication	Lesion for definition of positive ICA	QUADAS-2 quality analysis criteria
Baker et al[23]	8	4	0	14	74	35.1%	Cirrhotic patients in pre-LT evaluation with cardiac risk factors	High risk patients/ positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Kryzhanovski et al[24]	0	1	0	0	63	1.6%	Cirrhotic patients in pre-LT evaluation with cardiac risk factors	High risk patients/ positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Senzolo et al[25]	0	2	0	0	24	8.3%	Cirrhotic patients in pre-LT evaluation	Positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Kandiah et al[26]	1	4	0	5	93	10.7%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Oprea-Lager et al[27]	1	1	0	0	156	1.2%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Davidson et al[28]	7	24	12	40	83	100%	Cirrhotic patients in pre-LT evaluation with cardiac risk factors	High risk patients/ positive MPS	> 70%	RB: P + I + R + F + AC: P + I + R +
Aydinalp et al[29]	6	34	0	64	389	26.7%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	> 50%	RB: P + I + R + F + AC: P + I + R +
Zoghbi et al[30]	2	11	2	12	87	31%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	> 70%	RB: P – I + R + F + AC: P – I + R +
Bezinover et al[31]	3	1	3	9	173	9.2%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	NA	RB: P + I + R + F + AC: P + I + R +
Bhutani et al[32]	20	46	12	215	414	70.7%	Cirrhotic patients in pre-LT evaluation	High risk patients/ positive MPS	> 70%	RB: P + I + R + F + AC: P + I + R +

TP: True positive; FP: False positive; FN: False negative; TN: True negative; ICA: Invasive coronary angiography; LT: Liver transplantation; MPS: Myocardial perfusion scintigraphy; NA: Not available; QUADAS-2: Quality assessment of diagnostic accuracy studies-2; RB: Risk of bias; P: Patient selection; I: Index text; R: Reference standard; F: Flow and timing; AC: Applicability concerns.

84.2%).

DISCUSSION

It is essential to understand the role of CAD in cirrhosis and LT patients. There is a need to improve pre-LT diagnostic tools because the age of LT candidates is rising and the proportion of NASH patients has been increasing. This systematic review is the largest current meta-analysis of diagnostic data for DSE and MPS in pre-LT patients. It increases the data available in a previous study of DSE as a diagnostic and prognostic tool for LT candidates, published by Nguyen *et al*[33], which found that DSE had a high negative predictive value for adverse outcomes post-LT.

Among the general population, a prior meta-analysis of five studies found that both DSE and MPS are accurate for detection of CAD, with sensitivity of 85% and specificity of 87%[34] for DSE and sensitivity of 83% and specificity of 77% for MPS[35]. However, this meta-analysis found much lower sensitivity values for diagnosis of CAD in patients awaiting LT, while specificity rates did not vary so much. This could have happened because results for stress testing might be false due to modifications in hemodynamics caused by ESLD, such as high-output cardiac failure, cirrhotic cardiomyopathy, anemia and the use of beta blockers[36,37].

Nevertheless, the most used method for pre-LT cardiac stress testing is DSE, since cirrhotic patients have a low tolerance of exercise[38]. When compared to ergometric cardiac stress testing, DSE has higher sensitivity (67% *vs* 88%) and specificity (71% *vs* 83%)[39-41]. The prognostic value of MPS has also been evaluated previously, with a hazard ratio of 3.17 for all-cause mortality for a group with reversible perfusion
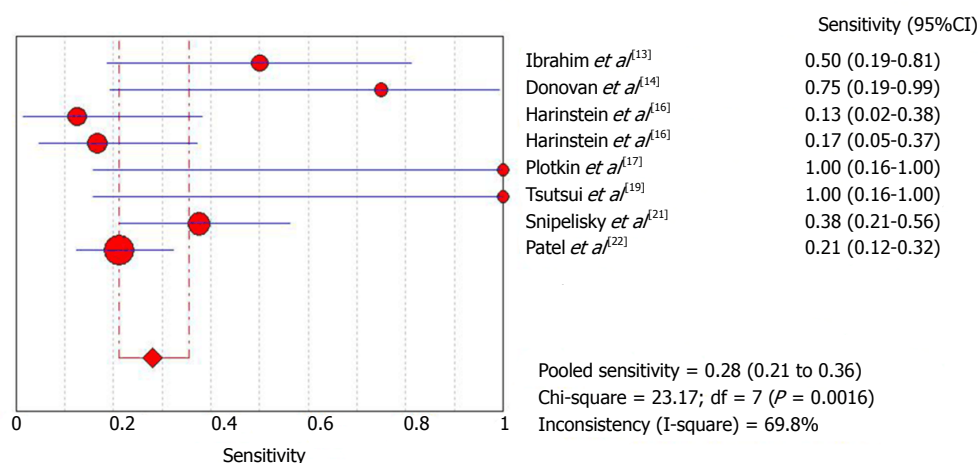
Figure 1 Forest plot for sensitivity meta-analysis - dobutamine stress echocardiography.
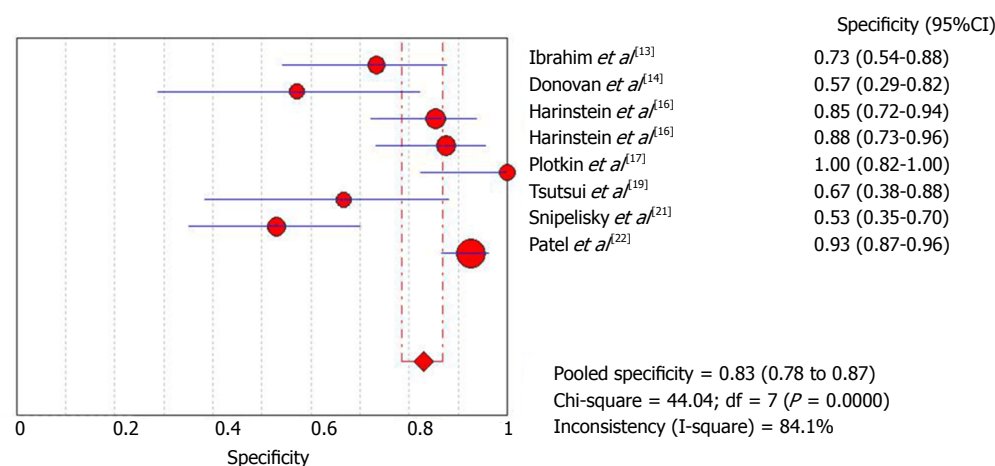
	Sensitivity (95%CI)
Ibrahim *et al*[13]	0.50 (0.19-0.81)
Donovan *et al*[14]	0.75 (0.19-0.99)
Harinstein *et al*[16]	0.13 (0.02-0.38)
Harinstein *et al*[16]	0.17 (0.05-0.37)
Plotkin *et al*[17]	1.00 (0.16-1.00)
Tsutsui *et al*[19]	1.00 (0.16-1.00)
Snipelisky *et al*[21]	0.38 (0.21-0.56)
Patel *et al*[22]	0.21 (0.12-0.32)

Pooled sensitivity = 0.28 (0.21 to 0.36)
Chi-square = 23.17; df = 7 (*P* = 0.0016)
Inconsistency (I-square) = 69.8%

Figure 2 Forest plot for specificity meta-analysis - dobutamine stress echocardiography.

	Specificity (95%CI)
Ibrahim *et al*[13]	0.73 (0.54-0.88)
Donovan *et al*[14]	0.57 (0.29-0.82)
Harinstein *et al*[16]	0.85 (0.72-0.94)
Harinstein *et al*[16]	0.88 (0.73-0.96)
Plotkin *et al*[17]	1.00 (0.82-1.00)
Tsutsui *et al*[19]	0.67 (0.38-0.88)
Snipelisky *et al*[21]	0.53 (0.35-0.70)
Patel *et al*[22]	0.93 (0.87-0.96)

Pooled specificity = 0.83 (0.78 to 0.87)
Chi-square = 44.04; df = 7 (*P* = 0.0000)
Inconsistency (I-square) = 84.1%

defect when compared to a group without perfusion defect[27].

The goal of both tests is to detect significant CAD prior to LT. In a high risk cohort in whom all patients underwent ICA and half had arterial systemic hypertension or diabetes, a 60% prevalence of CAD was found - one third with severe disease. Presence of moderate to severe CAD was associated with the presence of two or more cardiac risk factors[2]. If needed, ICA and stenting, seem to be safe in cirrhotic patients, taking precaution with the doubling of antiplatelet blockade in patients with esophageal varices[42]. The presence of CAD is associated with a poorer prognosis post-LT[43-45], although, Wray *et al*[6] did not detect a change in prognosis in the cohort they described. One must keep in mind also that pre-LT cardiac evaluation is costly and is not free from risks. In a previous study by Fili *et al*[46], the study protocol failed to demonstrate improvement in prognosis, but did raise

costs.

One meta-analysis has found that DSE is superior to MPS among patients undergoing major vascular surgery - a positive DSE meant higher relative risk for perioperative MACE and all-cause mortality, when compared to MPS[47]. The prognostic role of DSE and MPS in patients undergoing kidney transplantation has been studied by two meta-analyses, which found these tests to be accurate in predicting outcomes, with DSE performing better than MPS in their analysis. Nevertheless, in this context, a normal non-invasive stress test did not necessarily exclude the possibility of adverse cardiac outcomes[48,49].

Analyzing the data collected and presented in this meta-analysis, it can be concluded that DSE and MPS offer limited accuracy for predicting CAD diagnoses. They both have low sensitivity and moderate specificity, which does not make them the ideal tests for pre-LT cardiac risk evaluation, as they also do
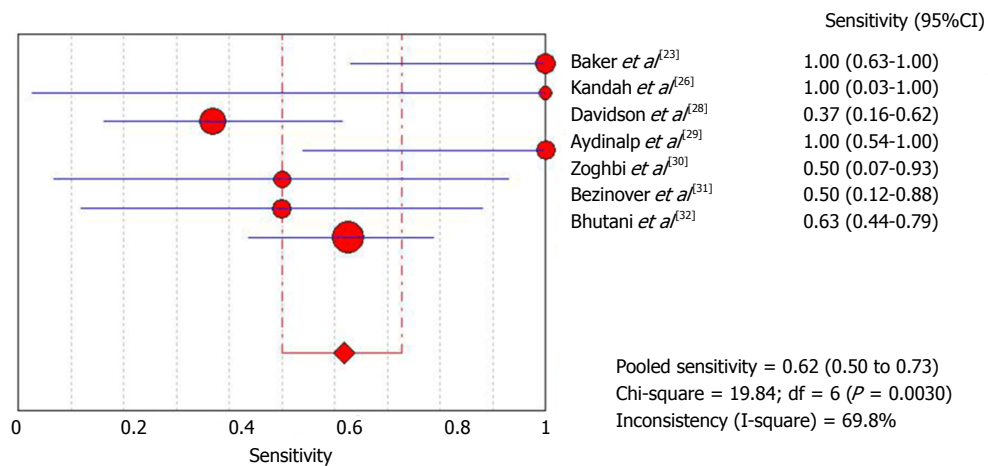
Figure 3 Forest plot for sensitivity meta-analysis - myocardial perfusion scintigraphy.
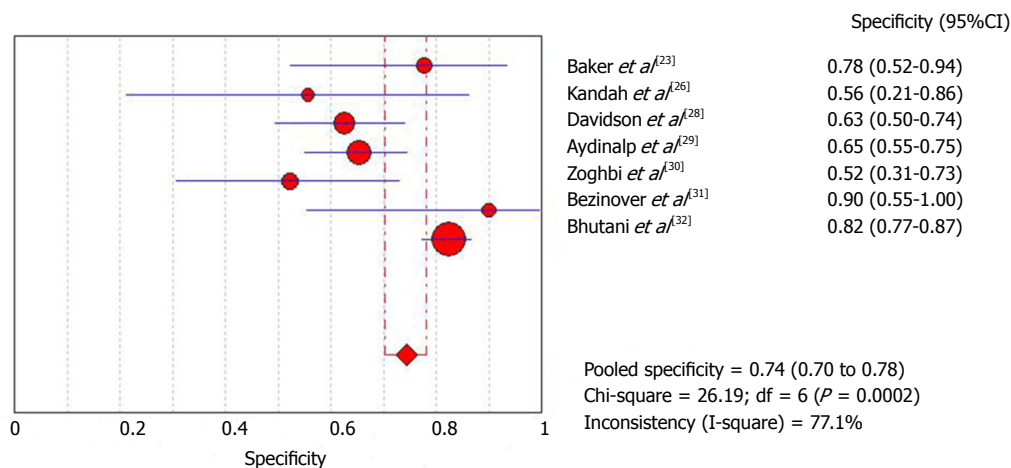

Figure 4 Forest plot for specificity meta-analysis - myocardial perfusion scintigraphy.

not predict adverse outcomes with accuracy[50]. This is consistent with the latest ACC/AHA guidelines, which describes non-invasive stress testing as of low sensitivity and specificity for detecting CAD in liver-transplant candidates[9]. Nevertheless, the high specificity found in this meta-analysis show that both DSE and MPS are useful for identifying patients with CAD. Notwithstanding, a negative stress test does not exclude the presence of CAD.

The element most likely to affect the results of this meta-analysis is selection of patients with indications for both LT and ICA. Generally, physicians happen to be more cautious in referring sicker and older patients for LT, which might mean that this group of patients is under-represented in this meta-analysis. Also, ICA is generally ordered only for high-risk patients with a positive DSE or MPS, and a positive ICA can lead to de-listing for LT, or even death before LT, due to advanced heart conditions.

This heterogeneity of indications for DSE and

MPS as part of pre-LT evaluation is reflected in the heterogeneity found in this meta-analysis, which is high throughout. Sub-analyses and meta-regressions were attempted in order to minimize heterogeneity, but with no substantial success. A major limitation is that, in most studies, just a few patients were referred for ICA, generally those with higher risk or a positive non-invasive stress test, which might over represent the proportion of CAD in pre-LT patients.

The results of this meta-analysis call into question the AASLD rationale of recommending routine non-invasive stress testing in pre-LT cardiac evaluation, since DSE and MPS both have low sensitivity for detecting CAD and did not predict outcomes ade-quately. Nevertheless, further prospective studies with standardized and homogenous patient charac-teristics are necessary in order to arrive at a better understanding of the value of pre-LT cardiac evaluation and a better-grounded decision on whether it is more cost-effective to follow AASLD[8] or ACC/AHA reco-

mmendations[9]. Initiatives such as development of the CAR-OLT score might help clarify this problem[10]. This paper's strengths are its complete search strategy, performed in multiple databases. Nevertheless, results are just for pre-LT candidates; hence only patients referred for LT because of ESLD were reviewed.

The results of this systematic review and meta-analysis can also have been limited due to a post-referral bias, since patients with previously known serious cardiac conditions are generally not referred for LT. Early revascularization, in the general population, might lead to a significant change in the history of CAD and a better survival. This is somewhat unclear for ESLD patients. Because of the small number of studies and their limitations, the quality of evidence in the meta-analysis was low throughout, which might have negatively impacted this review.

In conclusion, this meta-analysis found that among few and limited studies, DSE and MPS are of limited value for predicting positive ICA. Their low sensitivity might make them inadequate for pre-LT cardiac evaluation. Prospective studies with larger samples are needed to better define an adequate test for predicting CAD in pre-LT patients.

ARTICLE HIGHLIGHTS

Research background
The concept of cardiac involvement with coronary artery disease (CAD) in cirrhotic patients has been changing as patients listed for liver transplantation (LT) have become older and sicker. A previous study of dobutamine stress echocardiography (DSE) as a diagnostic and prognostic tool for LT candidates, published by Nguyen *et al*, which found that DSE had a high negative predictive value for adverse outcomes post-LT. This study tries to elucidate the problem of CAD screening in pre-LT patients.

Research motivation
There is a real need for protocols for cardiac evaluation of patients awaiting LT - particularly for cirrhotic patients. The American Association for the Study of Liver Diseases (AASLD) published a guideline in 2005 that recommends myocardial stress testing for every patient referred for LT. Nevertheless, the guideline published in 2012 by the American Heart Association (AHA and the American College of Cardiology (ACC), suggested that myocardial stress testing should be reserved for patients with three or more CAD risk factors. Better understanding the use of these tools might lead to better choices for pre-LT patients and better prognosis post-LT.

Research objectives
To evaluate the diagnostic value of DSE and myocardial perfusion scintigraphy (MPS) in predicting CAD in cirrhotic patients listed for LT, using invasive coronary angiography (ICA) as gold-standard. This could help clinicians choose the best test for predicting adverse cardiac events post-LT.

Research methods
A systematic review and meta-analysis was performed. Searches were run on the electronic databases Scopus, Web of Science, EMBASE, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Library for Systematic Reviews and Opengray.eu. There was no language or date of publication restrictions. The reference lists of the studies retrieved were searched manually.

Research results
The search strategy retrieved 322 references for DSE and 90 for MPS. In the final analysis, 10 references for DSE and 10 for MPS were included. Pooled sensitivity was 28% and 61% for DSE and MPS and specificity was 82% and 74%, for diagnosis of CAD using ICA as gold-standard, respectively.

Research conclusions
This study found that DSE and MPS do not have adequate sensitivity for determination of whether CAD is present, despite having significant specificity. There is a need for better tools in order to detect CAD in pre-LT patients. It is not feasible to determine whether AASLD or AHA/ACC is correct, hence both tests underperformed. It is proposed a hypothesis that new methods, tests or scores are need in order to clarify this question, which could impact pre-LT decisions in the future.

Research perspectives
It is possible to conclude that current evidence regarding pre-LT cardiac stress testing is lacking, and future research are bound to focus into solving this important clinical question. A comprehensive study, cohort or randomized, is necessary in order to gather more information on the utility and feasibility of the use of current and future tests in order to determine the presence of pre-LT CAD.

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